inter alia, in the paragraph spanning page 6 and page 7, first full paragraph on page 8, starting at the full paragraph on page 11 to last full paragraph on page 12, in the paragraph starting at the bottom of page 14, and in second full paragraph on page 17. Support in the specification for claims 43- 47, 51-53 and 55-58, and 61-63 is found, *inter alia*, at the middle of page 7, the bottom of page 15, and the bottom of page 18. Support in the specification for claims 48- 50, and 58-64 is found, *inter alia*, starting at the bottom of page 7 to the end of first full paragraph of page 8.

In response to the objection to the Sequence Listing a new Sequence Listing correcting the deficiencies accompanies this response. The Office Action requests that a copy of the Notice accompany the replacement Sequence Listing to Comply. However, no Notice to Comply was sent by the Patent & Trademark Office with the Office Action. In lieu of the Notice to Comply, Applicant attaches hereto a copy of the Raw Sequence Listing Error Summary, for the convenience of the Examiner.

Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

Claims 1-3, 6-8, 13, 15-18, 20-21, 23-27, 29, 30, 32-34, 36-40 are rejected under 35 U.S.C. § 112, first paragraph as not enabled. The Office Action asserts that the invention's claims are directed to gene therapy for treatment of auto-immune disorders. The Office Action cites a report by Orkin and Motulsky, *Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy*, (1995) (hereafter, Orkin) and Verma and Somia, *Nature* 389: 239-242 (1997) (hereafter, Verma) in support of the proposition that gene therapy is a highly unpredictable form of the art.

Applicant respectfully traverses. The applicant claims a method comprising the steps of removing APC cells from a patient, transferring into the cells a polynucleotide encoding all or an antigenic portion of a protein to which the patient's antigen specific T cells respond, reintroducing the engineered APC cells into the patient and, further administering a product detrimental to activated T cell proliferation. This is an *ex vivo* treatment, very different from gene therapy *in vivo*, or gene replacement therapy. The Office Action mistakenly focuses on a general assessment of the state of the art in the

field of gene therapy, emphasizing shortcomings in methods for *in vivo* targeted gene delivery, the sustained expression at high levels of introduced genes, and targeting of particular cells usually required for *in vivo* gene therapy.

In assessing the major problems of gene therapy at the time of the report, Orkin observes that the major stumbling block is an inadequate understanding of the biological interaction of the vectors with the hosts. See paragraph 3, page 1 of the report. In its recommendations on page 2, under the first paragraph, the panel recommends concentrating efforts to "enhancing and maintaining high level expression of genes transferred to somatic cells, achieving tissue specific and regulated expression of transferred genes and directing genes transferred to specific cell types." In the section entitled "The Rationale for Gene Therapy of Human Disease" a description of the various gene therapy targets is given. The emphasis is overwhelmingly on gene replacement and infection by viral vectors *in vivo*. For example, it is stated that *in vivo* "gene addition" is limited by the need for delivery to specific cell types and high level expression (page 5). Orkin further states that "current means for transferring DNA do not provide feasible strategies for reaching [tumorigenic] cells that have spread widely in the body" (page 6). Such problems relate only to *in vivo* gene transfer. The most significant difficulty Orkin attributes to *ex vivo* treatment is that "it is not yet known what cell types to target, much less how they will be isolated, treated, and returned to the patient." *Id,* page 6. The present invention, however, specifically teaches targeting APCs.

Verma also relates primarily to *in vivo* gene replacement. It teaches that "[most of the current gene therapy approaches make use of ... viral vectors." The most serious limitation, is that "humans have an immune system to fight off the virus, and our attempts to deliver genes into viral vectors have been confronted by the host responses." An additional limitation Verma teaches is the need to identify/target specific host cells (page 239). The article informs that current vectors for gene delivery have some limitations which make each of them unsuitable for all utilities. However, the problem is limited because "the choice of vector would be dictated by the specific therapeutic need.". See table on page 241.

However, Verma also teaches that phase 1 clinical trials studies have demonstrated that major toxicity problems are not associated with delivery systems and the article predicts that "in the not to distant future, gene therapy will become as routine a practice as heart transplants are today." Verma *supra,* end of article at page 242.

The Office Action's reliance on Orkin and Verma are misplaced in that those articles are concerned with general evaluation of the merits and ramifications of *in vivo* gene therapy. However, those general concerns do not apply to the present invention. The claimed methods employ *ex vivo,* not *in vivo* gene transfer, contrary to the assertions in the Official Action. ("Removing antigen presenting cells (APCs)... transferring into the APCs a polynucleotide...." Claim 41.) Thus, the method inserts a polynucleotide into isolated APCs. Therefore, issues such as targeting *in vivo* to specific cells or the effect of the immune response by the host on the delivery vector are not germane to the invention.

The Office Action asserts that no working example has been provided for construction of a Vaccinia virus to be used for therapy and that "use of an expression vector to transfect cultured cells is not sufficient to provide enablement for APC cells transfected with the vaccinia viral vector in vivo." The specification, however, clearly indicates that the invention is drawn to "*in vitro* preparations into which DNA has been inserted *ex vivo*." Page 8, first full paragraph. No genetic therapy *in vivo,* as suggested in the Office Action, is claimed.

Moreover, the specification teaches the use of transduced or transfected APCs throughout the specification, and clearly documents how to use viral vectors for transfection. In particular, the specification teaches that "any virus capable of introducing exogenous desired DNA to the antigen presenting cells can be used." Page 7, last paragraph. The Vaccinia virus vector is given as a particular example. The specification describes preparation of Vaccinia virus constructs, in addition to plasmid vector constructs. The viral constructs described include constructs with antigen and signal and transmembrane/cytoplasmic tail portions from the Lamp1 genes, and constructs with a product which would be detrimental to propagation of activated T-cells. The specification provides the source of the genetic elements and examples of actual

engineered viral vectors. See page 8.

The Office Action further asserts that "no enablement is given for expression of gene fragments that would induce a therapeutic response." See page 6 of the Office Action. The specification, however, teaches that the "extra cellular portion of the α-subunit (comprising amino acids 1-120), is believed to comprise the epitopes to which most AchR-specific T cells respond. Thus, this portion is believed to be sufficient as the presented antigen for the antigen presenting cells." Page 6, last paragraph. Thus gene fragments are taught and enabled.

Further, the rejection states that use of cultured cells is not taught. See paragraph spanning pages 6 and 7 of the Office Action. Selection of transfected cells, however, is described in the Examples. See page 12, last paragraph. Assays to test transfected cells for the desired activities are also provided. For example, a lymphoproliferation assay is presented on page 13 of the specification, as well as an assay for killing antigen-stimulated T-cells, both by Fas ligand or antibodies to Fas. Thus the specification teaches the use of cultured cells, contrary to the assertion of the Office Action.

In light of these explanations, withdrawal of the rejection of claims under § 112, first paragraph is respectfully requested.

Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

Claims 1, 2, 3, 6, 7, 8, 13, 15, 16, 17, 18, 20, 21, 23, 25, 26, 27, 33, 34, 36, and 38 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite. All these claims have been canceled and replaced with generally parallel claims 41-67. The Applicant does not agree that all the questioned terms were indefinite. However, for the sake of prosecuting the application in a timely manner, the Applicant has replaced the objected terms to meet the Examiner's objections. However, a comment is required in regard to rejection of former claim 36, now claim 63. The Office Action asserts that "it is not clear as to what part of the FADD protein would accomplish the function of protection." See page 8.

Claims should be read in light of the guidance in the specification. A truncated

FADD is described throughout the specification. A particular genetic element described as a truncated FADD is designated as NFD4 and its source is indicated. *See inter alia*, page 8 of the specification. The specification further lists a number of expression vectors in which the element was used. A further explanation as to the nature of the truncated FADD is provided at the end of the first full length paragraph on page 8 which states that, "[T]he truncated FADD is an amino terminal truncation which is dominant negative that prevents Fas ligand/Fas mediated apoptosis." The application teaches that such a truncated FADD is sufficient to prevent apoptosis, and that the functional domain of the FADD is at the N-terminal. The specification provides a source for truncated FADD and an assay to determine alternative functional forms of truncated FADD. In light of those disclosures, "truncated FADD" is not an indefinite expression. The relevant claims now recite "a truncated form of FADD wherein said truncated form is sufficient to protect a cell also expressing Fas from apoptosis." It is respectfully submitted that the recitation is clear in view of the teachings of the specification.

The Applicant respectfully requests that in light of the explanations and amendments the rejection of claims under 35 U.S.C. § 112, second paragraph be withdrawn.

The Rejection of Claims Under 35 U.S.C. § 102(e)

Claims 1-2, 16-18, 24, 29-30, 32, and 37 are rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,633,234. The Applicant respectfully traverses.

The applicant claims a method comprising the steps of removing APCs from a patient, transferring into the APCs a polynucleotide encoding all or an antigenic portion of a protein to which the patient's antigen specific T cells respond, reintroducing the engineered APC cells into the patient and, further, administering a product detrimental to activated T cell proliferation. Other claims are directed to transduced or transfected APCs, and still other claims are directed to recombinant viruses. The APCs comprise (a) a first polynucleotide sequence encoding a protein comprising all or a portion of an auto-antigen to which the patient's antigen-specific T cells respond, said all or a portion

of an auto-antigen being functionally connected to a signal peptide and a transmembrane/cytoplasmic tail, whereby endosomal processing of said all or a portion of the auto-antigen is facilitated, and (b) a second polynucleotide sequence which encodes a product detrimental to proliferation of activated T cells. The virus infects human APCs and comprises (a) a first polynucleotide sequence which encodes all or a portion of an auto-antigen to which an auto-immune disease patient's antigen-specific T cells respond, and (b) a second polynucleotide sequence which encodes a product detrimental to proliferation of activated T cells.

The '234 patent teaches a targeting signal for directing proteins to the endosomal/lysosomal cell compartment resulting in more effective presentation of an antigen via the MHC class II molecules and thus providing enhanced *in vivo* stimulation of $CD4^+$ T cells specific for the antigen. The '234 patent concludes that "delivering antigens to an endosomal/lysosomal compartment by means of chimeric constructs containing such lysosomal targeting signals will be of value in any vaccination or immunization strategy that seeks to stimulate $CD4^+$ MHC class II restricted immune responses." See end of abstract. The '234 patent does not teach or suggest destruction of T cells as claimed by applicant, but rather teaches the specific *stimulation* of T cells. Clearly, the step of administering a product detrimental to activated T cell proliferation is not described in patent '234. Similarly the element of a polynucleotide encoding a product detrimental to activated T cell proliferation is not taught for either APCs nor for a virus which infects APCs.

In light of this explanation, the Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. § 102(e).

It is respectfully urged that the present claims are in condition for allowance. Notice to that effect is earnestly solicited. Should there be any questions in regard to this application, Examiner Sorbello is invited to contact the undersigned.

Respectfully submitted,

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